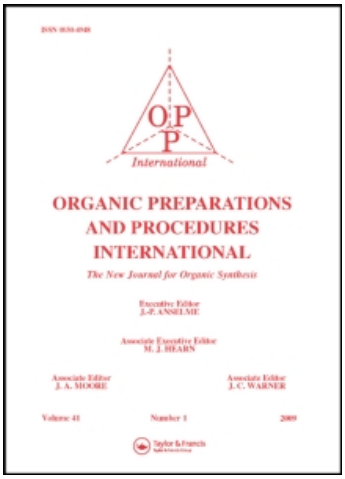


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# N-SULFONYL LACTAMS *via* SULFONATION OF LACTIM ETHERS

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# N-SULFONYL LACTAMS *via* SULFONATION OF LACTIM ETHERS†

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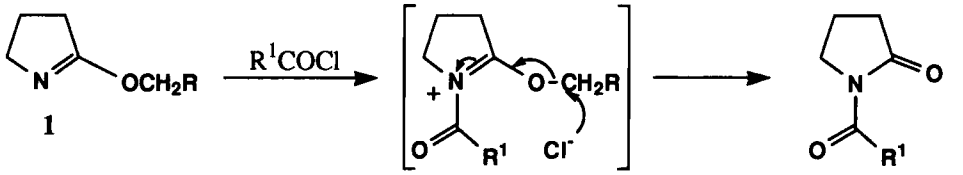
Sulfonamides are a common protecting group for amines but have been used sparingly for lactams.[1] Indeed, there are few true protecting groups for lactams.[1b] Literature methods for the preparation of *N*-sulfonyl lactams are also sparse and the two most common methods are the cyclization of sulfonylamino acids[2] and the Beckmann rearrangement of hydroxylamines derived from cyclic ketones[3] or the corresponding O-sulfonylhydroxylamines.[4] O-Tosyl lactim ethers have also been shown to rearrange to the corresponding *N*-tosyl lactams.[5] These synthetic methods rely on indirect reactions to form the sulfonyl lactam. The cyclization procedures are useful for the preparation of small ring lactams but not of large ones. The ring expansion techniques are useful for a variety of systems, but require either the formation or the availability of the cyclic ketone precursors prior to rearrangement. This can be a problem with large ring systems and a "direct" sulfonation method would be very attractive.

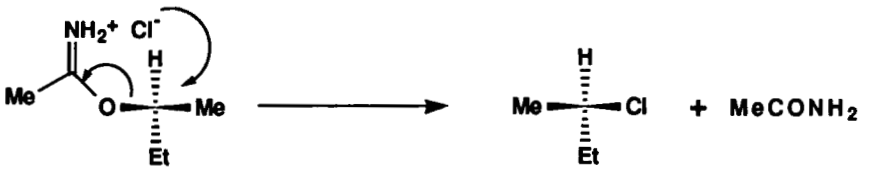
We therefore sought a more direct and efficient method for the preparation of *N*-sulfonyl lactams. Lactim ethers such as **1** are attractive precursors since they were reported to react with acyl chlorides, producing *N*-acyl lactams (**3**) in good yield.[6] The reaction is generally believed to proceed *via* initial formation of an *N*-acyl iminium salt (**2**), followed by displacement of the lactam (which




a) R = H b) R = Me **1** **2** **3**

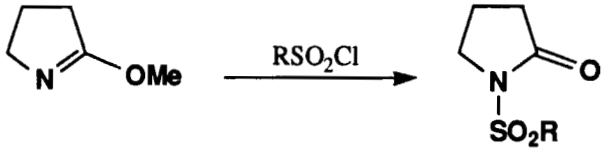
behaves as a leaving group) by attack of the chloride ion. 1-Alkylacetimidate chlorides (such as **4**) also react in this manner and the reaction was shown by McElvain and Tate[7] to be first order with respect to disappearance of the halide ion. Stevens, Morrow and Lawson showed that **4** decomposed upon heating to give optically active *sec*-butyl chloride (**5**).[8] This reaction occurred with inversion of

configuration at the chiral carbon in **4**, consistent with $S_N2$ attack by chloride at the α-carbon of imidate **4**. Acetamide was the by-product of this thermolysis reaction. We believed this approach was




**4** **5**

**TABLE 1.** Effects of Solvent and Temperature on the Sulfonation of 2-Methoxypyrroline (**1a**)



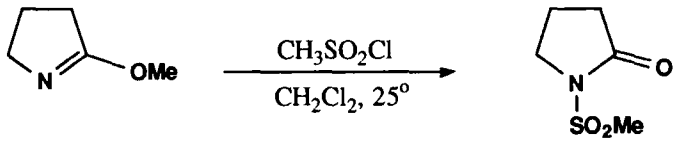

**1a** **6**

| Solvent | R | Temp. (°C) | Lactam (%) |
|---|---|---|---|
| $CH_2Cl_2$ | $-CH_3$ | 25 | 76 (**6a**) |
| | | 40 | 79 |
| | -Ph | 25 | 76 (**6b**) |
| | | 40 | 76 |
| | *p*-Tolyl | 25 | 72 (**6c**) |
| | | 40 | 70 |
| THF | $-CH_3$ | 25 | 0 |
| | -Ph | 25 | 0 |
| | *p*-Tolyl | 25 | 0 |
| Benzene | $-CH_3$ | 25 | 0 |
| | | 80 | 0 |
| | -Ph | 25 | 0 |
| | | 80 | 0 |
| | *p*-Tolyl | 25 | 0 |
| | | 80 | 0 |
| DMF | $-CH_3$ | 25 | 0 |
| | | 153 | 80 (**6a**) |
| | -Ph | 25 | 0 |
| | | 153 | 74 (**6b**) |
| | *p*-Tolyl | 25 | 0 |
| | | 153 | 73 (**6c**) |

amenable to formation of *N*-sulfonyl lactams from sulfonyl chlorides and lactim ethers. Cremlyn[9] had previously shown that lactams react with benzenesulfonyl chloride (benzene, ambient temperature, triethylamine) to give the O-phenylsulfonyl lactam but, to our knowledge, the analogous

reaction of sulfonyl halides with lactim ethers had not been explored. We therefore prepared 2-methoxypyrroline (**1a**) from 2-pyrrolidinone and dimethyl sulfate. Initial reaction of **1a** with methanesulfonyl chloride in refluxing benzene gave no trace of the desired sulfonyl lactam. Other changes in the reaction conditions[10] failed to produce the desired sulfonyl lactam. When dichloromethane was used as a solvent at ambient temperatures, however, an 80% yield of *N*-methanesulfonyl-2-pyrrolidinone (**6**) was obtained.

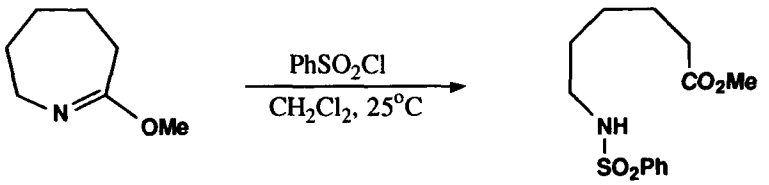
Reaction of lactim ether **1a** with benzenesulfonyl chloride and *p*-tosyl chloride also gave good yields of the *N*-sulfonyl lactam (see Table 1). We prepared 2-ethoxypyrroline (**1b**) and showed that reaction with methanesulfonyl chloride, under the same conditions used with **1a**, failed to give the sulfonyl lactam. The reaction produced a small amount of ethyl 4-aminobutyrate but primarily gave recovered **1b**. Attack at the methylene group of O-ethyl of **1b** is expected to be significantly slower than at the O-methyl group of **1a**. Identical results were observed when methanesulfonyl chloride reacted with 2-ethoxy-3,4,5,6-tetrahydropyridine (**7b**). We next extended this methodology to lactim ethers derived from lactams of larger size rings, including tetrahydropyridin-2-ones (**12a-12c**), 2H-hexahydro-azepin-2-ones (**13a-13c**), 1H-hexahydroazacin-2-one and 2H-octahydroazonin-2-one.




**1a** **6a**



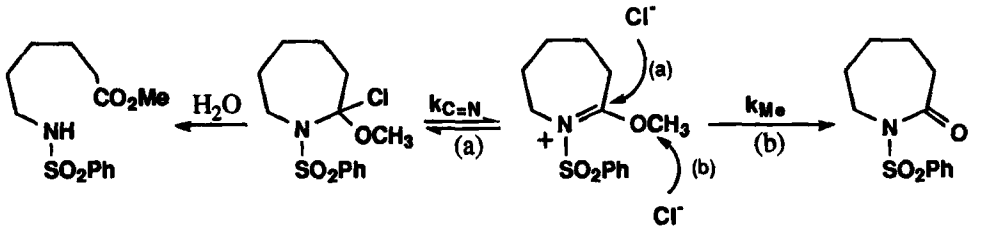
In each case, reaction with dimethyl sulfate or trimethyloxonium tetrafluoborate provided the lactim ether. In all cases we found that other than **1a**, the reaction with methanesulfonyl chloride, benzenesulfonyl chloride or *p*-toluenesulfonyl chloride led to significant amounts of *N*-sulfonyl amino ester, derived from opening of the ring. For example, reaction of **8** gave a 78% yield of **15**.




**8** **15**

Our working hypothesis for the ring opening was that attack at methyl was slow relative to nucleophilic attack by chloride at the iminium carbon with larger rings, which led to ring opening. This could also be true for the pyrrolidinone derivatives but the equilibrium generated by opening to the amino ester probably favored the ring, in accord with well known observations in five-membered ring systems.[11] If the sulfonation reaction requires nucleophilic attack on the methyl group, increasing

the concentration of chloride should enhance that $S_N2$ attack, increasing the yield of sulfonyl lactam. Indeed, addition of one equivalent tetrabutylammonium chloride to the dichloromethane solution of lactim ether **8** and benzenesulfonyl chloride led to an increase in the yield of sulfonyl lactam **12b** from 0% to 52%.[12] We found that the addition of one equivalent of tetrabutylammonium chloride, bromide or iodide (TBAI) was sufficient to give moderate to good yields of the sulfonyl lactam, as shown in Table 2. We noted no significant change in the yield of sulfonated products as the halide counterion was varied from tetrabutylammonium chloride to bromide to iodide. We believe a competition between $k_{Me}$ (attack at the O-methyl) vs. $k_{C=N}$ (attack at the iminium carbon) dominates this reaction and that an equilibrium such as that shown for **15** ← **16** ⇌ **17** → **12b** is established in all reactions. In the case of pyrroline derivatives (**1**), attack at the iminium carbon may be preferred but the equilibrium favors the ring closed product (lactam), as noted above.[11] With larger



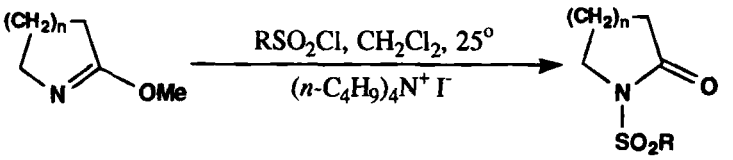

**15** **16** **17** **12b**

ring lactim ethers, attack at C=N opens the ring and the equilibrium favors the open chain amino ester. Addition of the ammonium halide may enhance the rate of attack at methyl ($k_{Me}$), favoring the sulfonyl lactam as the major product in all cases. An alternative explanation is that increasing the concentration of halide increases the rate at which the equilibrium is achieved. Attack on methyl may be of a different order with respect to the halide than ring opening. The presence of trace amounts of water in the ammonium halide may also be important for conversion of the iminium salt to the lactam. The by-product of each reaction in Table 2 was the *N*-sulfonylamino ester, which was easily separable from the target lactam by chromatography. Addition of tetrabutylammonium halides to the reaction allowed the preparation of very large ring sulfonyl lactams, often difficult to obtain *via* cyclization techniques.

This reaction represents the best method reported for the "direct" sulfonation of large ring lactams. This two-step procedure relies on the formation of a 2-methoxy lactim ether from the lactam, which is easy under a variety of conditions. The subsequent mild conditions for conversion to the sulfonyl lactam are applicable to a wide range of lactams of various size rings. *N*-Sulfonyl lactams are now readily accessible by a convenient and general synthetic route.

**Acknowledgements.**- We thank Pfizer Inc. for providing monies for summer support of undergraduate research *via* the Pfizer Undergraduate Summer Scholarship. We also thank Mr. Marvin Thompson who recorded the mass spectra of all compounds in this work.

**TABLE 2.** Sulfonation of Lactim Ethers with Sulfonyl Chlorides and Tetrabutylammonium Iodide




| n | Lactim | R | % | Lactam |
|---|---|---|---|---|
| 1 | **1a** | $CH_3$ | 76 | **6a** |
| | | Ph | 76 | **6b** |
| | | *p*-Tolyl | 72 | **6c** |
| 2 | **7** | $CH_3$ | 73 | **11a** |
| | | Ph | 66 | **11b** |
| | | *p*-Tolyl | 66 | **11c** |
| 3 | **8** | $CH_3$ | 62 | **12a** |
| | | Ph | 62 | **12b** |
| | | *p*-Tolyl | 62 | **12c** |
| 4 | **9** | $CH_3$ | 63 | **13a** |
| | | Ph | 57 | **13b** |
| | | *p*-Tolyl | 60 | **13c** |
| 5 | **10** | Ph | 59 | **14** |



## EXPERIMENTAL SECTION

All $^1H$ NMR and $^{13}C$ NMR were obtained on an IBM 270-WY instrument at 270.133 MHz or 67.925 MHz, respectively. All chemical shifts are reported in ppm, downfield from tetramethylsilane. The infrared spectra were recorded on a Perkin-Elmer IR-28S instrument and mass spectra were obtained on an HP 5985 GC-MS system. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. TLC was carried out on silica gel 60F-254 sheets and column chromatography on silica gel 60 (70-230 mesh), both from E. Merck. All lactim ethers were prepared from the corresponding lactams. The 2-pyrrolidinone, tetrahydropyridin-2-one, 2H-hexahydroazepin-2-one, 1H-hexahydroazocin-2-one and 2H-octahydroazonin-2-one precursors were obtained from Aldrich. Dimethyl sulfate, diethyl sulfate, epichlorohydrin, boron trifluoride etherate, dimethyl ether, THF, DMF, tetrabutylammonium iodide, *p*-toluenesulfonyl chloride, benzenesulfonyl chloride and methanesulfonyl chloride were also obtained from Aldrich. The diethyl ether, dichloromethane, pentane and benzene solvents were obtained from Baker. All ethers were dried (Na/benzophenone) and distilled under argon prior to use. Benzene and dichloromethane were also dried (distilled from $CaH_2$ or $P_2O_5$ respectively) prior to use. The trimethyloxonium and triethyloxonium tetrafluoroborates were prepared by the method of Meerwein[13] from dimethyl or diethyl ether, boron trifluoride etherate and epichlorohydrin.

### Preparation of Lactim Ethers

**Procedure (A).**- A three neck round-bottomed flask, equipped with a condenser and pressure equalizing addition funnel, was charged with lactam (0.10 mol). Addition of 0.15 mol of dimethyl sulfate was followed by heating to 60~100° for 15 hrs (oil bath). The reaction mixture was poured into ice

cold saturated $K_2CO_3$ solution (100 mL), extracted with of 50:50 ether-pentane (3x100 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried ($K_2CO_3$) and the solution was concentrated *in vacuo* (T ≤ 20°). The lactim ether was purified by distillation or by chromatography on silica gel.

**Procedure (B).**- A 50 mL round-bottomed flask was charged with 20 mmol of lactam, 20 mmol of trimethyloxonium tetrafluoroborate[13] and 25 mL of dry dichloromethane. The mixture was stirred overnight at room temperature and diluted with 75 mL of dichloromethane. The dichloromethane solution was extracted with 2 x 25 mL of ice cold saturated $K_2CO_3$, once with 25 mL of water and once with 25 mL of saturated brine. The dichloromethane solution was dried ($K_2CO_3$) and the solvents were removed *in vacuo* (T ≤ 20°). The lactim ether was purified by distillation or by chromatography on silica gel.

**2-Methoxypyrroline (1a).**- Reaction of 2-pyrrolidinone (8.5 g, 99.9 mmol) and dimethyl sulfate (18.9 g, 149.8 mmol) by *procedure A* gave 2-methoxypyrroline (6.2 g, 63% yield) , bp. 117°, lit.[14a,d] bp. 118-120°. $^1$H NMR ($CDCl_3$): δ 2.03 (quintet, 2H, *J* = 7.8 Hz), 2.45 (t, 2H, *J* = 7.9 Hz), 3.66 (t, 2H, *J* = 7.2 Hz) and 3.80 ppm (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 23.4 (t), 30.9 (t), 55.0 (t), 55.4 (q) and 173.9 ppm (s); IR (neat): 2950, 2873, 16586, 1440, 1349, 1307, 1254, 1006 and 688 cm$^{-1}$.



**2-Ethoxypyrroline (1b).**- Reaction of 2-pyrrolidinone (8.5 g, 99.9 mmol) and diethyl sulfate (23.1 g, 150 mmol) by *procedure A* gave 2-ethoxypyrroline (10.0 g, 88% yield), bp. 128°, lit.[14a,15] bp. 133-137°; $^1$H NMR ($CDCl_3$): δ 1.31 (t, 3H, *J* = 7.2 Hz), 2.01 (quintet, 2H, *J* = 6.6 Hz), 2.45 (t, 2H, *J* = 8.7 Hz), 3.66 (t, 2H, *J* = 7.0 Hz) and 4.20 ppm (q, 2H, *J* = 7.1 Hz); $^{13}$C NMR ($CDCl_3$): δ 14.5 (q), 23.1 (t), 31.2 (t), 55.1 (t), 63.8 (t) and 173.1 ppm (s); IR (neat): 2950, 2873, 1658, 1403, 1349, 1307, 1254, 1006 and 688 cm$^{-1}$.

**6-Methoxy-2,3,4,5-tetrahydropyridine (7a).**- Reaction of δ–valerolactam (2.0 g, 20.2 mmol) and trimethyloxonium tetrafluoroborate (3.8 g, 20.3 mmol) by *procedure B* gave **7a** (2.10 g, 92% yield), bp. 53°, 20 mmHg (lit.[14e,f] bp. 48°, 15 mmHg); $^1$H NMR ($CDCl_3$): δ 1.56 (m, 2H), 1.73 (m, 2H), 2.15 (t, 2H, *J* = 6.6 Hz), 3.40 (t, 2H, *J* = 5.7 Hz) and 3.63 ppm (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 20.4 (t), 22.5 (t), 25.9 (t), 46.8 (t), 51.8 (q) and 163.0 ppm(s); IR (neat): 2943, 1684, 1438, 1347, 1220, 1020, 936 and 6589 cm$^{-1}$.

**6-Ethoxy-2,3,4,5-tetrahydropyridine (7b).**- Reaction of δ-valerolactam (2.0 g, 20.2 mmol) and triethyloxonium tetrafluoroborate (3.8 g, 20.0 mmol) by *procedure B* gave **7b** (2.29 g, 89% yield), bp 56°, 20 mmHg lit.[16] bp. 86-88°; $^1$H NMR ($CDCl_3$): δ 1.12 (t, 3H, *J* = 7.08 Hz), 1.80 (m, 4H), 2.35 (m, 2H), 3.28 (m, 2H) and 3.41 ppm (q, 2H, *J* = 7.1 Hz); $^{13}$C NMR ($CDCl_3$): δ 12.2 (q), 21.5 (t), 23.3 (t), 32.4 (t), 47.2 (q), 53.6 (t) and 169.2 ppm(s); IR (neat): 2943, 1684, 1438, 1347, 1220, 1020, 936 and 658 cm$^{-1}$

**7-Methoxy-3,4,5,6-tetrahydro-2H-hexahydroazepin-2-one (8).**- Reaction of 2H-hexahydroazepin-2-one (2.2 g, 19.4 mmol) and trimethyloxonium tetrafluoroborate (3.0 g, 20.3 mmol) by *procedure B* gave **8** (2.32 g, 94% yield), bp. 58°, 20 mmHg (lit.[14c,17] bp. 60-65°, 13 mmHg); $^1$H NMR ($CDCl_3$): δ

1.54 (m, 4H), 1.77 (m, 2H), 2.40 (m, 2H), 3.41 (m, 2H) and 3.58 ppm (s, 3H);[13]C NMR ($CDCl_3$): δ 23.3 (t), 27.8 (t), 31.1 (t), 31.9 (t), 48.6 (t), 52.3 (q) and 169.5 ppm (s); IR (neat): 2928, 2849, 1684, 1440, 1365, 1344, 1248, 1188, 1147 1086, 1039, 999, 801, 744 and 688 $cm^{-1}$.

**2-Methoxy-3,4,5,6,7,8-hexahydroazacine (9)**.- Reaction of 3,4,5,6,7,8-hexahydro-2-azacinone (2.5 g, 19.7 mmol) and trimethyloxonium tetrafluoroborate (3.0 g, 20.3 mmol) by *procedure B* gave **98** (2.66 g, 96% yield), bp. 61°, 5 mmHg (lit.[17c] bp. 48-53°, 2.0 mmHg); $^1$H NMR ($CDCl_3$): δ 1.40 (m,2H), 1.48 (m, 2H), 1.66 (m, 4H), 2.35 (t, 2H, $J$ = 5.7 Hz), 3.46 (t, 2H, $J$ = 5.7 Hz) and 3.63 ppm (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 22.2 (t), 23.9 (t), 26.5 (t), 27.6 (t), 28.8 (t), 29.3 (t), 48.4 (t), 52.3 (q) and 169.5 ppm (s); IR (neat): 2927, 2861, 1682, 1457, 1278, 1206, 1110, 1084 and 760 $cm^{-1}$.

**2-Methoxy-3,4,5,6,7,8,9,10-octahydro-2H-azonine (10)**.- Reaction of 3,4,5,6,7,8-hexahydro-2-azoninone (3.0 g, 21.2 mmol) and trimethyloxonium tetrafluoroborate (3.0 g, 20.3 mmol) by *procedure B* gave **10** (2.75 g, 87% yield), bp. 72°, 5 mmHg (lit.[17a] bp. 44-46°, 0.5 mmHg); $^1$H NMR ($CDCl_3$): δ 1.47 (m,4H), 1.68 (m, 6H), 2.31 (m, 2H), 3.41 (m, 2H) and 3.63 ppm (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 24.6 (t), 26.1 (t), 27.6 (t), 28.0 (t), 31.1 (t), 31.6 (t), 47.1 (t), 52.3 (q) and 167.0 ppm (s); IR (neat): 2929, 1681, 1456, 1256, 1222, 1145, 1102, 1058, 823 and 766 $cm^{-1}$.



**General Procedure for the Preparation of N-Sulfonyl Lactams**.- A 25 mL round-bottomed flask was charged with lactim ether (5.0 mmol), 10.0 mmol of methanesulfonyl chloride, benzenesulfonyl chloride or toluenesulfonyl chloride and dry dichloromethane (5 mL). After addition of 5.0 mmol of tetrabutylammonium iodide (or bromide or chloride), the mixture was stirred at room temperature for 16 hours, filtered and the sulfonyl lactam product isolated by silica gel chromatography (200 mL of 50:50 pentane-dichloromethane, 100 mL dichloromethane and 100 mL of ether). The preferred conditions are tetrabutylammonium iodide in 100 mL of $CH_2Cl_2$ at ambient temperature.

**1-Methylsulfonyl-2-pyrrolidinone (6a)**.- A mixture of 2-methoxypyrroline (**1a**, 0.50 g, 5.0 mmol) and methanesulfonyl chloride (1.20 g, 10.5 mmol) in $CH_2Cl_2$ gave of **6a** (0.67 g, 76%yield, $R_f$ = 0.3, $CH_2Cl_2$/silica gel).[18] $^1$H NMR ($CDCl_3$): δ 2.16 (m, 2H), 2.59 (t, 2H, $J$ = 8.3 Hz), 3.28 (s, 3H) and 3.89 ppm (s, 2H, $J$ = 7.0 Hz); $^{13}$C NMR ($CDCl_3$): δ 16.3 (t), 32.2 (t), 40.5 (t), 46.6 (t) and 173.8 ppm (s); IR (neat): 3017, 2937, 1732, 1420, 1330, 1154, 1121, 1026, 981, 627, 526 and 512 $cm^{-1}$.

**1-Benzenesulfonyl-2-pyrrolidinone (6b)**.- A mixture of 2-methoxypyrroline (**1a**, 0.50 g, 5.0 mmol) and benzenesulfonyl chloride (1.80 g, 10.5 mmol) in $CH_2Cl_2$ gave of **6b** (0.85 g, 76% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel).[19] $^1$H NMR ($CDCl_3$): δ 2.09 (quintet, 2H, $J$ = 7.6 Hz), 2.44 (t, 2H, $J$ = 8.20 Hz), 3.91 (t, 2H, $J$ = 7.0 Hz), 7.56 (m, 2H), 7.63 (m, 1H) and 8.04 ppm (m, 2H); $^{13}$C NMR ($CDCl_3$): δ 18.1 (t), 32.1 (t), 47.2 (t), 127.9 (d, 2C), 129.0 (d, 2C), 134.0 (d), 138.0 (s) and 173.3 ppm (s); IR (neat): 2925, 1732, 1485, 1418, 1171, 1116, 1021, 962, 736, 686, 602, 581 and 543 $cm^{-1}$.

**1-(4-Methylbenzenesulfonyl-2-pyrrolidinone (6c)**.- A mixture of 2-methoxypyrroline (**1a**, 0.50 g, 5.0 mmol) and *p*-toluenesulfonyl chloride (1.80 g, 9.4 mmol) gave of **6c** (0.87 g, 72% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel).[2c,20] $^1$H NMR ($CDCl_3$): δ 2.07 (quintet, 2H, $J$ = 7.6 Hz), 2.42 (t, 2H, $J$ = 8.2 Hz), 2.44 (s, 3H), 3.89 (t, 2H, $J$ = 7.0 Hz), 7.34 (d, 2H, $J$ = 8.0 Hz), and 8.04 ppm (d, 2H $J$ = 8.1 Hz); $^{13}$C

NMR ($CDCl_3$). δ 18.2 (t),21.7 (q), 32.2 (t), 47.3 (t), 128.0 (d, 2C), 129.7 (d, 2C), 135.2 (s), 145.2 (s) and 173.4 ppm (s); IR (neat): 2916, 1731, 1595, 1418, 1355, 1119, 962, 815, 715, 665, 601 and 559 $cm^{-1}$.

**1-Methanesulfonyl-3,4,5,6-tetrahydropyridin-2-one (11a)**.- A mixture of 2-methoxy-3,4,5,6-tetrahydropyridine (**7a**, 0.50 g, 4.4 mmol) and methanesulfonyl chloride (1.00 g, 8.7 mmol) gave of **11a** (0.57 g, 73% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel).[18,20] $^1H$ NMR ($CDCl_3$): δ 1.63 (m, 2H), 1.92 (m, 2H), 2.58 (t, 2H, *J* =7.2 Hz), 3.13 (s, 3H) and 3.76 ppm (t, 2H, *J* = 4.8 Hz); $^{13}C$ NMR ($CDCl_3$): δ 20.4 (t), 23.1 (t), 38.6 (t), 41.8 (t), 46.1 (q) and 176.2 ppm (s); IR (neat): 3015, 2936, 1733, 1421, 1331, 1156, 1124, 1024, 980, 625, 526 and 513 $cm^{-1}$.

**1-Benzenesulfonyl-3,4,5,6-tetrahydropyridin-2-one (11b)**.- A mixture of 2-methoxy-3,4,5,6-tetrahydropyridine (**7a**, 0.50 g, 4.4 mmol) and benzene-sulfonyl chloride (1.6 g, 9.1 mmol) gave of **11b** (0.69 g, 66% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel).[22] $^1H$ NMR ($CDCl_3$): δ 1.65 (m, 2H), 1.90 (m, 2H), 2.57 (t, 2H, *J* =7.2 Hz) 3.76 (t, 2H, *J* = 4.8 Hz), 7.50 (m, 2H), 7.62 (m, 1H) and 8.01 ppm (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 20.4 (t), 23.1 (t), 38.6 (t), 41.8 (t), 127.8 (d, 2C), 129.1 (d, 2C), 134.1 (d), 137.9 (s) and 173.2 ppm (s); IR (neat): 2926, 1731, 1483, 1142, 1170, 1118, 1022, 960, 735, 687, 602, 579 and 542 $cm^{-1}$.



**1-(4-Methylbenzenesulfonyl)-3,4,5,6-tetrahydropyridin-2-one (11c)**.- A mixture of 2-methoxy-3,4,5,6-tetrahydropyridine (**7a**, 0.50 g, 4.4 mmol) and toluenesulfonyl chloride (1.7 g, 8.9 mmol) gave of **11c** (0.74 g, 66% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel).[4,20] $^1H$ NMR ($CDCl_3$): δ 1.66 (m, 2H), 1.97 (m, 2H), 2.43 (s, 3H), 2.57 (t, 2H, *J* =7.4 Hz), 3.76 (t, 2H, *J* = 5.0 Hz), 7.34 (d, 2H, *J* = 8.1 Hz), and 8.04 ppm (d, 2H *J* = 8.1 Hz); $^{13}C$ NMR ($CDCl_3$): δ 20.4 (t), 21.6 (q), 23.1 (t), 38.6 (t), 41.8 (t), 128.0 (d, 2C), 129.7 (d, 2C), 135.2 (s), 145.2 (s) and 173.5 ppm (s); IR (neat): 2918, 1730, 1598, 1490, 1336, 1119, 961, 715, 663, 601 and 560 $cm^{-1}$.

**1-Methanesulfonyl-2H-hexahydroazepin-2-one (12a)**.- A mixture of 3,4,5,6-tetrahydro-7-methoxyazepine (**8**, 0.50 g, 3.9 mmol) and methanesulfonyl chloride (0.9 g, 7.9 mmol) gave of **12a** (0.45 g, 62 % yield, $R_f$ = 0.3 in $CH_2Cl_2$/ silica gel).[18] $^1H$ NMR ($CDCl_3$): δ 1.78 (m, 6H), 2.66 (m, 2H), 3.33 (s, 3H) and 3.91 ppm (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 23.1 (t), 29.1 (t), 29.4 (t), 38.8 (t), 42.5 (t), 45.9 (t) and 176.4 ppm (s); IR (neat): 2935, 1695, 1341, 1256, 1162, 959, 881, 778, 630 and 515 $cm^{-1}$.

**1-Benzenesulfonyl-2H-hexahydroazepin-2-one (12b)**.- A mixture of 3,4,5,6-tetrahydro-7-methoxyazepine (**8**, 0.50 g, 3.9 mmol) and benzenesulfonyl chloride (1.4 g, 7.8 mmol) gave of **12b** (0.60 g, 62% yield, $R_f$ = 0.3 in $CH_2Cl_2$/ silica gel).[22] $^1H$ NMR ($CDCl_3$): δ 1.71 (m, 4H), 1.84 (m, 2H), 2.54 (m, 2H) and 4.04 (m, 2H), 7.54 (3H, m) and 7.99 ppm (2H, m).; $^{13}C$ NMR ($CDCl_3$): δ 22.9 (t), 29.4 (t), 38.8 (t), 46.5 (t), 53.5 (t), 128.5 (t) and 128.6 (d, 2C), 133.5, 139.6 (s) and 174.8 ppm (s); IR (neat): 2925, 1711, 1481, 1419, 1172, 1114, 1019, 916, 739, 602, 580 and 544 $cm^{-1}$.

**1-(4-Methylbenzene)sulfonyl-2H-hexahydroazepin-2-one (12c)**.- A mixture of 3,4,5,6-tetrahydro-7-methoxyazepine (**8**, 0.50 g, 3.9 g mmol) and toluenesulfonyl chloride (1.5 g, 7.9 mmol) gave of

**12c** (0.63 g, 62% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel).[2a,b,4,21] $^1H$ NMR ($CDCl_3$): δ 1.72 (m, 4H), 1.83 (m, 2H), 2.42 (s, 3H), 2.53 (m,2H), 4.02 (m, 2H), 7.30(d, 2H, *J* = 8.3 Hz), and 7.87 ppm (d, 2H, *J* = 8.3 Hz); $^{13}C$ NMR ($CDCl_3$): δ 21.6 (q), 22.9 (t), 29.2 (t), 29.3 (t), 38.8 (t), 46.4 (t) and 128.5 (d, 2C), 129.2 (d, 2C), 136.6 (s), 144.5 (s), and 174.8 ppm (s); IR (neat): 2917, 1173, 1599, 1492, 1352, 1118, 959, 818, 720, 661, 603 and 562 $cm^{-1}$.

**1-Methanesulfonyl-3,4,5,6,7,8-hexahydroazacin-2-one (13a).**- A mixture of 3,4,5,6,7,8-hexahydro-2-methoxyazacine (**9**, 0.50 g, 3.5 mmol) and methanesulfonyl chloride (0.8 g, 7.0 mmol) gave of **13a** (0.46 g, 63% yield, $R_f$ = 0.3, $CH_2Cl_2$/silica gel). $^1H$ NMR ($CDCl_3$): δ 1.60 (m, 4H), 1.79 (m, 2H), 1.90 (m, 2H), 2.66 (t, 2H, *J* = 6.4 Hz), 3.33 (s, 3H) and 3.98 ppm (t, 2H, *J* = 6.0 Hz); $^{13}C$ NMR ($CDCl_3$): δ 25.8 (t), 26.1 (t), 28.7 (t), 30.8 (t), 36.3 (t), 42.7 (t), 45.5 (t) and 176.5 ppm (s); IR (neat): 2938, 1686, 1654, 1596, 1542, 1508, 1342, 1162, 1119 and 510 $cm^{-1}$.

*Anal.* Calcd. for $C_8H_{15}NSO_3$, (205.0773). Observed 205.0778 (± 1.0 mmu).

**1-Benzenesulfonyl-3,4,5,6,7,8-hexahydroazacin-2-one (13b).**- A mixture of 3,4,5,6,7,8-hexahydro-2-methoxyazacine (**9**, 0.50 g, 3.5 mmol) and benzenesulfonyl chloride (1.2 g, 6.8 mmol) in 5 mL gave of **13b** (0.54 g, 57% yield, $R_f$ = 0.3, $CH_2Cl_2$/silica gel). $^1H$ NMR ($CDCl_3$): δ 1.45 (m, 2H), 1.60 (m, 4H), 1.82 (m, 2H), 2.44 (m, 2H ), 3.70 (m, 2H) and 7.54 (m, 3H), and 7.88 ppm (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 24.5 (t), 25.9 (t), 27.4 (t), 33.0 (t), 34.0 (t), 43.4 (t), 127.0 (d, 2C) and 128.5 (d, 2C), 140.3 (d) and 174.7 ppm (s); IR (neat): 2925, 1722, 1491, 1420, 1172, 1116, 1020, 963, 733, 686, 582 and 541 $cm^{-1}$;

*Anal.* Calcd. for $C_{13}H_{16}NSO_3$, (P-1, 266.0851). Observed 266.0857 (± 1.3 mmu).

**1-(4-Methylbenzene)sulfonyl-3,4,5,6,7,8-hexahydroazacin-2-one (13c).**- A mixture of 3,4,5,6,7,8-hexahydro-2-methoxyazacine (**9**, 0.50 g, 3.5 mmol) and *p*-toluenesulfonyl chloride (1.3 g, 6.8 mmol) gave of **13c** (0.58 g, 60% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel). $^1H$ NMR ($CDCl_3$): δ 1.45 (m, 2H), 1.60 (m, 4H), 1.82 (m, 2H), 2.44 (m, 2H ), 3.70 (m, 2H) and 7.54 ppm (m, 3H), 7.88 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 24.5 (t), 25.9 (t), 27.4 (t), 33.0 (t), 34.0 (t), 43.4 (t), 127.0 (d, 2C) and 128.5 (d, 2C), 140.3 (d) and 174.7 ppm (s); IR (neat): 2923, 1720, 1600, 1492, 1353, 1118, 961, 818, 711, 662 and 557 $cm^{-1}$;

*Anal.* Calcd. for $C_{14}H_{19}NSO_3$, (281.1086). Observed 281.1087 (± 1.4 mmu).

**1-Benzenesulfonyl-3,4,5,6,7,8,9,10-octahydro-2-azoninone (14).**- A mixture of 3,4,5,6,7,8,9,10-octahydro-2-methoxyazonine (**10**, 0.5 g, 3.2 mmol) and benzenesulfonyl chloride (1.1 g, 6.2 mmol) gave of **14** (0.52 g, 59% yield, $R_f$ = 0.3 in $CH_2Cl_2$/silica gel). $^1H$ NMR ($CDCl_3$): δ 1.56 (m, 6H), 1.73 (m, 2H), 1.92 (m, 2H), 2.64 (m, 2H), 3.84 (m, 2H) and 7.55 ppm (m, 3H), 7.87 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 24.7 (t), 26.1 (t), 27.5 (t), 28.5 (t), 31.9 (t), 33.9 (t), 43.1 (t), 127.0 (d, 2C), 129.1 (d, 2C), 129.6 (s), 132.6 (d) and 174.1 ppm (s); IR (neat): 2927, 1725, 1495, 1420, 1172, 1117, 1020, 969, 607, 585 and 540 $cm^{-1}$;

*Anal.* Calcd. for $C_{14}H_{19}NSO_3$, (281.1086). Observed 281.1086 (± 1.4 mmu)

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